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Genetical Changes in Mice and Men*

BY DEFINITION AN adaptation is a change in the structure or function of an organism that makes it able to carry out a fuller range of activities than if the change had not occurred. This change can take place through a modification of the organism during its life, or it may be built in to the hereditary make-up of the individual, a population or a species. I am going to describe in this paper only *genetical* changes and, in particular, certain conditions which may lead to genetical changes and hence potential adaptations.

Now the easiest situation to investigate, from the genetical point of view, is a population which is variable with respect to some trait (and particularly if the trait is discontinuously distributed—or polymorphic—in the population), when it is possible to compare two organisms from the same place to see if either of them is better fitted to survive than the other in a given set of circumstances—in other words, whether the observed variation is adaptive.

Malaria and Sickle-cell Trait

This is exactly what Allison[1] did in East Africa. He inoculated with subtertian malaria fifteen Africans who had the sickle-cell trait of their red blood cells, and fifteen who had normal blood. Fourteen out of the fifteen with normal blood developed clinical malaria, but only two of the fifteen with sickle-cell trait did so. Allison interpreted this fact — together with demographic and haematological evidence (Figure 1)—as showing that sickling was an adaptation to life in malarial regions, in that the protection against malaria afforded to young children more than offset any disadvantage due to the possession of sickle-cell haemoglobin (there is evidence for an increased death rate in non-malarial areas of young sicklers when compared with non-sicklers).[41]

In this sort of situation it is possible to calculate fairly exactly what the advantage is to an individual to possess a particular adaptation. The incidence of sickle-cell trait reaches 40 per cent in some parts of central Africa. Since a quarter of the children of two sickle-cell trait individuals will suffer from sickle-cell disease (which is apparently always lethal under normal African conditions), and since this elimination of sickle-cell genes will have to be compensated for by sickle-cell trait people (heterozygotes for the gene) producing more children on average than normal people, it can be calculated that the heterozygotes have about a 30 per cent "advantage" over normal people.

Furthermore, it would be expected that the advantages of sickle-cell trait sufferers will disappear if they are protected against malaria-carrying mosquitoes. This is what was found by Lehmann and Raper.[32] Africans of higher social status have a lower incidence of sickling than their more primitive neighbours, apparently because the malarial death rate is greater where living conditions are unfavourable.

The same effect holds in the USA. When African Negroes were transported to the States about 300 years ago, they entered a largely malaria-free environment. The advantage

* A paper read at the Annual Meeting of the British Association for the Advancement of Science, Nottingham, 1966.

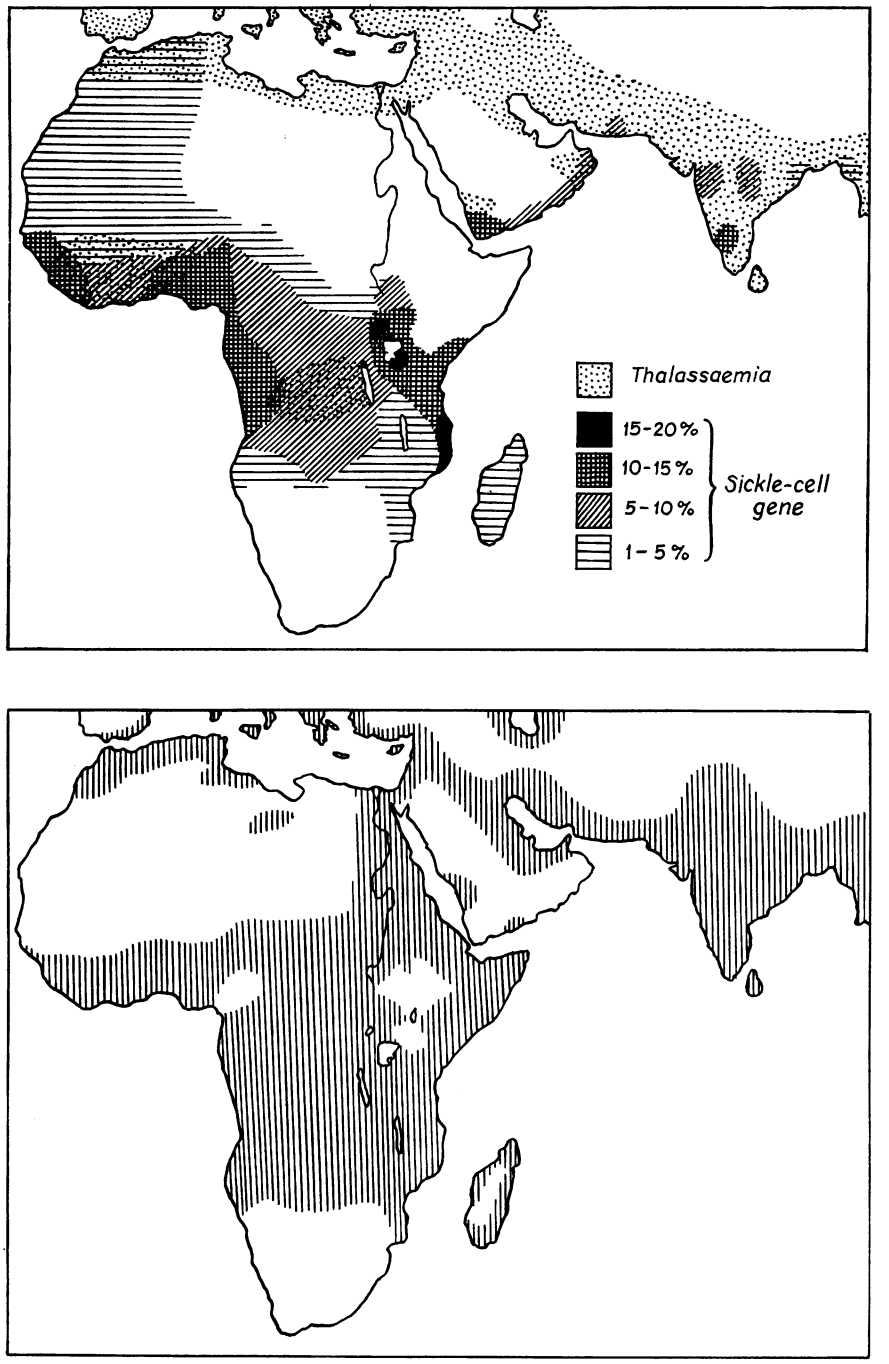

FIGURE 1

Distributions of malaria (below), and of haemoglobin S and thalassaemia (top picture).

of the sickle-cell heterozygote was lost, and the frequency of the sickle-cell gene has presumably been falling since then. The present incidence of sickle-cell trait among Negroes in the USA is about 9 per cent. Allison[2] estimated that the average incidence of sickling in the areas whence they originally came was at least 22 per cent, and that not more than one-third of the genes in the present Negro population have been introduced by marriage with non-Africans. This means that a fall in frequency of the trait from about 15½ to 9 per cent has taken place in about twelve generations as a result of the loss of selective advantage of the heterozygotes.

A similar situation exists in the distribution of carriers of the gene for glucose-6-phosphate dehydrogenase deficiency in Sardinia.[10] This is another gene which is thought to protect its carriers against malaria. The villages of the highly malarial (until 1946) west coast have a gene frequency as high as 35 per cent; villages on the central mountain plateau have an extremely low gene frequency (Figure 2). Blood group studies of villages on east and west coasts and in the mountains showed identical frequencies of the ABO, MN and Rh blood groups, suggesting that these populations were basically genetically similar. In other words, natural selection, acting through disease susceptibility, has devised a dimorphic situation at this one gene locus.

Genetical Constancy and Genetical Change

Now in the absence of any disturbing influences, the genetical composition of a population will remain constant—this is one way of expressing the so-called Hardy-Weinberg equilibrium. If a population shows genetical change in either time or space, it is possible to ask some fairly specific questions about that population to find out whether the change that has taken place is an adaptive or irrelevant one as far as the population is concerned. There are four forces which may cause the gene frequencies within a population to change. They are:

i. mutational changes in genes and chromosomes;
ii. natural selection favouring one phenotype under some of the conditions experienced by the population;
iii. genetical drift, that is random changes from generation to generation as a result of sampling errors in a population with a small number of breeding individuals; and
iv. migration into or out of a population of individuals not genetically typical of the population.

The sort of questions about the genetical influences on a population that may be asked and answered can be illustrated by a recent study of the evolution of an island population of the house mouse.[4]

The Pembrokeshire island of Skokholm was successfully colonized by mice only about sixty years ago. The evidence that there were no mice there before that is only anecdotal, but there is a strong local tradition to that effect. Mice on the island nowadays (Figure 3) are bigger and more fecund than mice on the neighbouring mainland—in other words they show features which have been used to distinguish many of the named sub-species of small mammals around the British Isles,[11, 29] and which might therefore be presumed to be adaptive (the coat colour differences frequently used to distinguish island races are often imprecise and of doubtful survival value). The size of the Skokholm mouse population fluctuates between about two or three hundred individuals in the spring to between two and ten thousand in the autumn (there is regularly an extremely heavy winter mortality) and since stabilizing selection may be quite strong (causing a reduction in skeletal variance of 20 to 30 per cent over the winter), the minimum population size is almost certainly too high for genetical drift to occur. When compared genetically with their nearest neighbours

and putative relatives—there is a story that mice were introduced in bedding for an animal being taken over to the island[34]—they are found to be very distinct.

Here we must digress to consider methods of genetically comparing populations. Old-time anthropologists used to place considerable reliance upon multivariate statistics based upon osteometric, and particularly craniometric, data. However, the genetics of skeletal size is difficult and the raw data need many adjustments to account for age, climate and nutritional differences etc.,[17] and the statistic generally used has been severely criticized.[20]

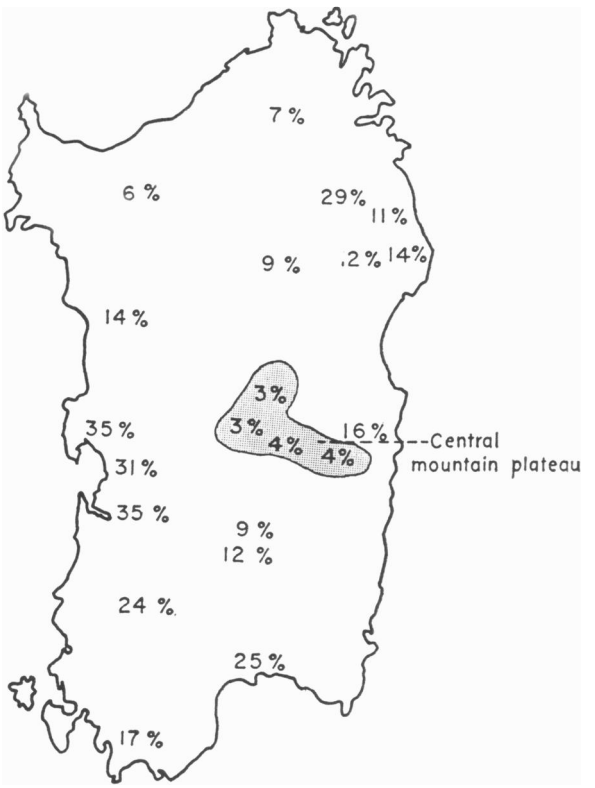

FIGURE 2

Frequency of the glucose-6-phosphate dehydrogenase deficiency gene in Sardinia (from Motulsky, A. and Campbell-Krant, J. M. in Blumberg, B. S. (Ed.) 1961. *q.v.* Neel.[41]

Therefore it is not surprising that nowadays physical anthropology relies so extensively on single gene polymorphic systems, like the blood groups and serum proteins. Nevertheless, there are considerable advantages in being able to compare populations on the basis of a large number of genes. Work on the morphology and genetics of the skeleton of the mouse by Grüneberg[25] has provided a method for doing this in terms of non-metrical or epigenetic variation, so that a "measure of divergence" can be computed as a measure of distinctiveness between two populations[3a]. Such a measure of distinctiveness has a number of genetical and computational advantages over other methods of calculating genetical differences.[6]

When mice from widely separated parts of the south of England and Wales are compared in terms of their measures of divergence they are found to be extremely like one another. This can only be due to stabilizing selection acting to maintain a favourable

phenotype. However, the Skokholm population is extremely distinct from its mainland neighbours (Figure 3). The obvious suggestion is that this divergence represents the

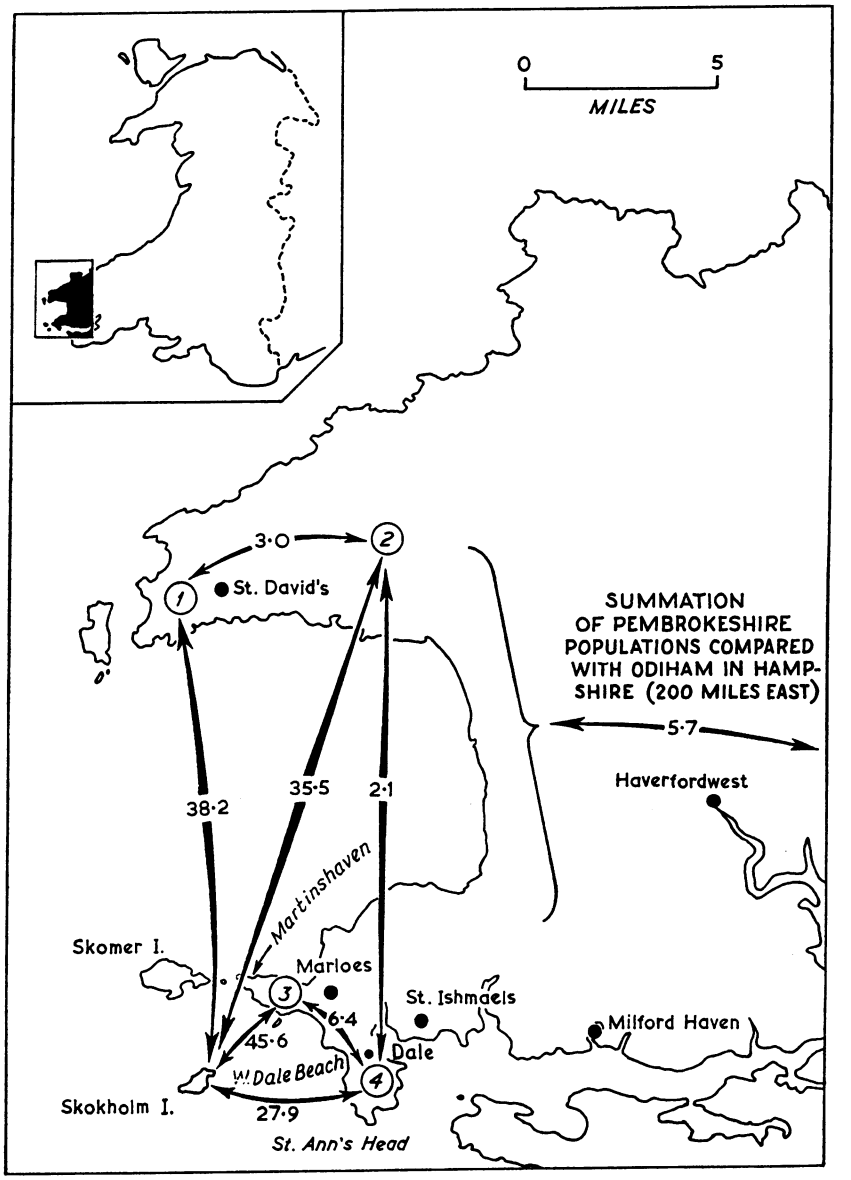

FIGURE 3

Measures of divergence based on skeletal data between Skokholm mice and neighbouring mainland animals (originally published in *Nature in Wales*, 1965, **9**, 3.).

consequences of adaptation of the mice to their island environment, and it is surprising that such a large divergence could have arisen in a space of about seventy years—around one hundred mouse generations.

Evolution by Mistake in Mice

This assumption is not borne out when Skokholm mice are compared with other mice from an ecologically similar island where the mice show similar differences in size, etc., from their near neighbours. The mouse population living under the closest approximation to Skokholm conditions that could be found was on the Isle of May in the Firth of Forth.

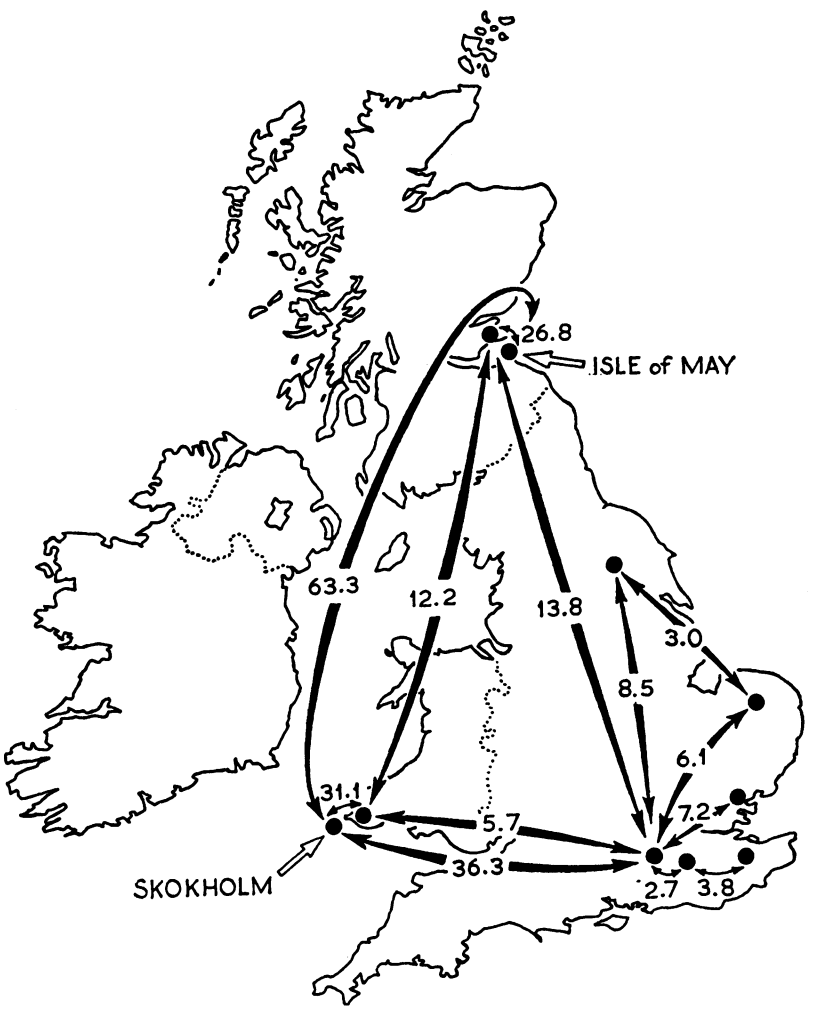

FIGURE 4

Measures of divergence based on skeletal data of Skokholm, Isle of May and sundry mainland mouse populations.

The origins of these mice are not known. The island has been fairly continuously occupied by man since the middle of the twelfth century, formerly by monks and smugglers, latterly by lighthouse keepers, but the earliest record of mice is in a letter written by a mid-nineteenth century lighthouse keeper: "We have no rats, but legions of mice, and

most impudent mice they are, for they sit and look in your face, and even gnaw at your trousers, with a composure that is most amusing". All we can say is that mice have been on the May for a longer time than they have been on Skokholm, that they are subjected to much the same environmental pressures, and that they may therefore be expected to be better adapted to island life than are the Skokholm animals.

Skeletal studies (Figure 4) show that the May mice are as distinct from their nearest mainland neighbours as are the Skokholm mice from their Pembrokeshire ones: their mean measure of divergence from four Fife populations was 26·8; of Skokholm from four Pembrokeshire ones was 31·1. The Fife populations had a divergence measure of 13·8 from southern English mice. However, the most significant comparison is that between the two island populations: the measure of divergence in this case was 63·3, effectively the sum of the divergences of the islands from their respective mainland neighbours, i.e. there is no evidence at all of any parallel adaptation in the Skokholm and May mouse populations. Natural selection has acted on the different gene-pools available on the two islands to produce two races of mice, each adapted to a similar set of conditions, but, one must presume, by different physiological mechanisms.

Isolated populations of mice are often quoted as being examples of particularly rapid evolutionary divergence. For example, twenty-seven different sub-species of small mammals have been described on different Scottish islands, and all these must have arisen since the end of the last Ice Age 8,000 years ago. A moment's reflection will show that there is no reason to suppose that the *actual rate of genetical change* in these races has been any quicker than normal. All these island races must have been founded by only a very few colonizers from the mainland. If a population of animals is genetically very heterogeneous—as seems to be generally accepted nowadays: it has been estimated that man is heterozygous at something like 30 per cent of his loci—it would be extremely unlikely that these few colonizers carried a representative sample of allelomorphs. This means that the isolated race would be different from the start, and any adaptation to local conditions that takes place will have to be by selection acting on the impoverished gene pool of the founders and their immediate descendants.

Delany[18] found that the characters which distinguish Hebridean races of the long-tailed field mouse, *Apodemus sylvaticus*, vary in an apparently completely random way among the different islands—as would be expected if they are mainly manifestations of the genetical make-up of their founders. Corbet[13] described a population of the bank vole (*Clethrionomys glareolus*) from a newly planted Forestry Commission plantation in Perthshire, 92 per cent of which had a tooth character (presence of a fourth loop on the inner surface of the third upper molar) which is only possessed by 29 per cent of the animals in a neighbouring plantation and throughout the rest of the Highlands (Figure 5). Now a high incidence of this particular character is found in many island forms, and has been used as one of the main distinguishing features of some "sub-species". However, the plantation where Corbet found the population was only planted in 1951 on what was previously an open grassy hillside unsuitable for *Clethrionomys*. Corbet concluded that the wood had been colonized by very few animals (perhaps only by a single pregnant female) which were unrepresentative for the area as far as that particular tooth character was concerned.

Under such circumstances, as Sewall Wright has pointed out, adaptive changes may take place fairly rapidly, because there will be no (or much less) immigration of animals bringing in gene combinations not highly suited to the local environment and which constantly disrupt locally evolved adapted gene complexes. This seems to be what has happened on both Skokholm and the Isle of May: the mice on the two islands have adapted to conditions on the islands, but adaptation has had to follow genetically different pathways, because different genes were available in the two places.

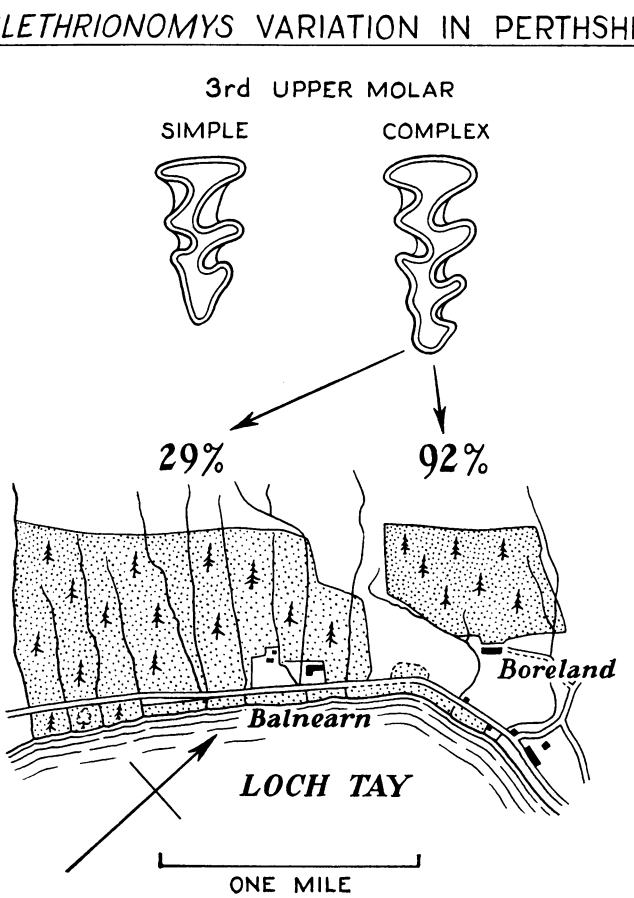

FIGURE 5

Map of an area on the north side of Loch Tay to show Boreland and Balnearn plantations (based on Corbet, 1963).

A Genetical Bottleneck in Snails

An example of the way isolation may cause genetical heterogeneity is provided by work of Goodhart[24] on the Hundred Foot Bank, an artificial earthen bank running alongside the New Bedford River near Ely. This twenty-mile-long waterway was dug in 1652 to take the River Ouse in a straight line across the Fens. The common snail *Cepaea nemoralis* occurs in large numbers along the bank. As far as can be seen, the environment of the snails is constant for several miles along the ten-foot-high grassy, sloping bank. A road runs alongside the bank in parts, and the vegetation below the road is much more variable than it is above it. Goodhart collected samples of snails at furlong intervals along a two-mile stretch of uniform bank. He found that the frequency of banding of the snails varied between 26 per cent and 76 per cent along the bank, and 26 per cent and 87 per cent along the verge below the road, the frequency of banding above and below the road tending to be similar despite the fact that there were greater differences in vegetation on the two sides of the road than along the whole length of the bank (Figure 6). Now the occurrence of

banding in *Cepaea* has been shown to be an adaptive character,[8, 22] both as a protective coloration against predation by birds (usually thrushes), and also as an indicator of heterotic vitality. Goodhart pointed out that the floods of 1947—the first serious ones in this area for over a century—must have drowned all the snails along the Bank except in isolated pockets. When the collections of snails were made by Goodhart five years later, the whole area had been recolonized, the roadside verge from the bank proper, but because the range of movement of snails is so small, the distribution of genes was still largely a reflection of the genetical constitution of the flood survivors. It is not impossible that the overall gene frequency is the same as prior to 1947, but this cannot be known. It will be interesting to learn of the genetical constitution of the snail population of this area in years to come.

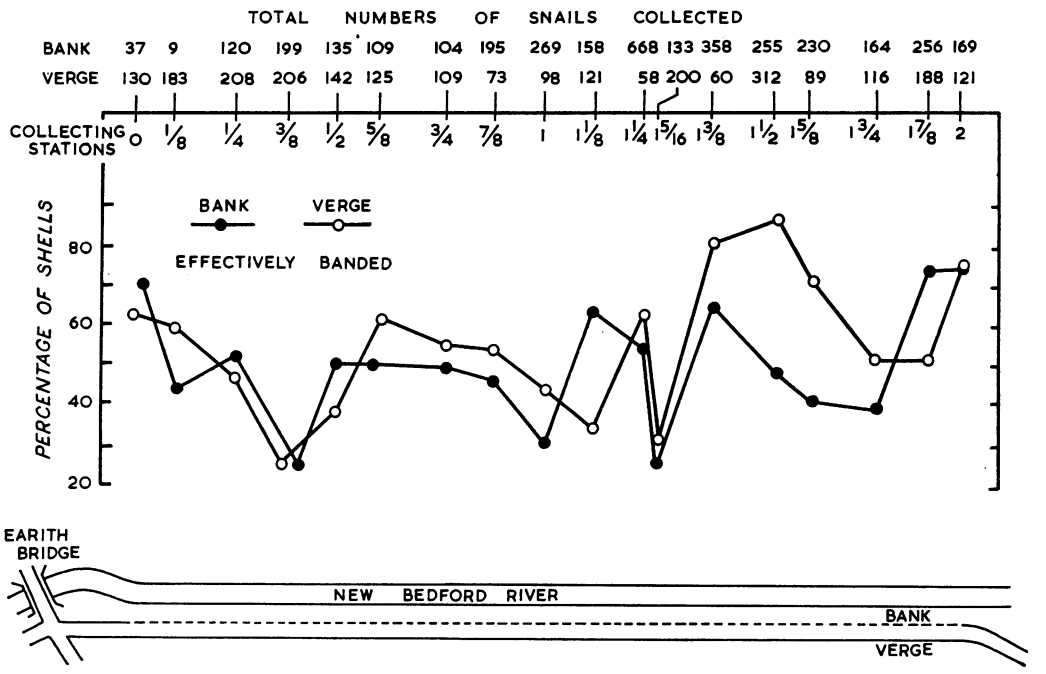

FIGURE 6

Distribution of frequencies of shell banding in *Cepaea* along the 100-foot bank (based on Goodhart, 1962)

In the case of Goodhart's snails, there was a "bottleneck" in the amount of genetical variability in a locality (Figure 7). This is exactly the same sort of founder effect that we have already discussed in relation to the colonization of islands. Although it is a chance effect on the genetical composition of the population—Waddington[53] describes it as *intermittent drift* in distinction to the more usually described although probably rarer *persistent drift* or Sewall Wright effect—it is one which could have beneficial effects on a population. For example, it is extremely difficult for a truly local adaptation to arise in the face of the constant immigration that takes place in any outbreeding population. Whereas there are plenty of clines in populations living on large land masses, it is only in genetical isolates (and that usually means an island for a terrestrial form) that differentiated forms are commonly found. Isolation of the organisms at one end of a cline may lead to a greater degree of adaptation—and hence success in terms of realized biomass—being possible. Furthermore, organisms isolated in this way are likely to possess a greater number

of locally advantageous allelomorphs than average, and hence natural selection has, it as were, a running start in the formation of an adaptation. The operation of the founder effect is a much more rapid and effectual mechanism of genetical change than is normal or "persistent" drift.

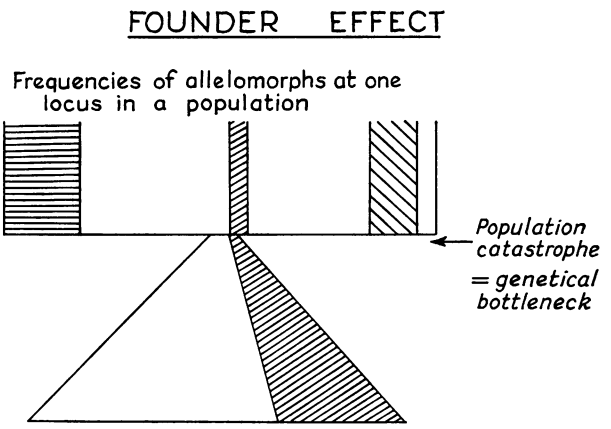

FIGURE 7
Diagram to show a genetical bottleneck.

Genetical Changes in Man

When we return from snails to man, examples of spectacular genetical changes or adaptations in the making are, not very surprisingly, more difficult to find. Stabilizing selection is certainly operating in human populations—the example usually quoted is Haldane's[97] analysis of Karn and Penrose's data on London birth weights, showing that three-fifths of all early post-natal death can be regarded as selection for an optimum weight, an effect which gives a selection coefficient of 2·7 per cent (the strength of this selection has become weaker in recent years[28])—and this is genetical change in each generation. Examples of the spread of genes resulting in local heterogeneity of the frequencies of particular allelomorphs are, however, more common.[23, 42]

As regards adaptive traits, advantageous genes will in most cases have already replaced other allelomorphs. We have already cited evidence relating to the low frequency of sickle-cell trait among American Negroes. Livingstone[33] has argued that the present distribution of abnormal haemoglobins has arisen relatively recently following the adoption by man of an agricultural existence and a relatively settled way of life, which, he maintains, is necessary for the evolution of holoendemic malaria. This means that the "antimalarial" genes found in different areas (haemoglobins S, C, and E; thalassaemia; and glucose-6-phosphate dehydrogenase deficiency) are not necessarily the most efficient genes for the purpose, and he adduces mathematical and circumstantial evidence that haemoglobin S may be spreading whatever other genes are present.

Huntington's Chorea

However, more direct examples of gene spread are available. Perhaps the best known concerns Huntington's chorea.[14] This is a dominantly inherited progressive atrophy of the central nervous system, which does not usually manifest until the fourth or fifth decade of life.[40] At this time a gradual falling-off in intellectual efficiency appears, often linked with

irritability or depression. Simultaneously the patient begins to show a general motor unrest, beginning with fidgeting and grimacing, proceeding to lack of co-ordination and choreiform movements, and eventually leading to complete helplessness and dementia. Death follows twelve to fifteen years after the start of the illness. By the time clinical symptoms appear, the affected person may have married and had a family. Half of the offspring of a sufferer will be afflicted. It is this unfortunate consequence that has caused this disease to be mentioned in many textbooks and become generally known.

The disorder is not common, but is distributed throughout the world, although it is almost entirely confined to the white races. However, the mutation which causes it seems to be a rare one, and affected persons usually occur in local concentrations, probably all deriving from a single mutated individual. For example, there are about 120 cases of Huntington's chorea in Tasmania. Each of these patients, together with some on the mainland of Australia, have a common ancestor, a Huguenot woman, who left her home in Somerset in 1848 to settle in Tasmania. She married twice, and choreics were recognized in her offspring from both husbands. In a small fishing-village in Ross-shire there are a number of cases of the disease, all stemming from a Cornish man who was one of Cromwell's soldiers.

The disease, however, is most common in the United States, where there must be at least 7,000 sufferers alive to-day. Genealogical research has enabled many scattered pockets of the disease as far spread as Hawaii, Nebraska, Oregon, California, Ohio and Iowa to be recognized as offshoots of New England stock which split when "the West was opened up" in the mid-nineteenth century (Figure 8). Almost all the American cases can be traced back to only three or four families, although the difficulties in tracing the origins of many of the earliest settlers—particularly those of lowly birth—is too difficult to permit dogmatism about their interrelationships.

However, at least two of the New England family groups can be traced back to three ancestors who all came from the village of Bures St. Mary on the Essex-Suffolk borders. Huntington's chorea has been present in this family from its earliest days in America although it was not recognized as a clinical and genetical entity until the mid-nineteenth century. No fewer than seven of the daughters or granddaughters of the original three immigrants were burnt at the stake for witch-craft, one of whom (Elizabeth Knapp) being described by the local minister as: "This pore and miserable object . . . observed to carry herselfe in a strange and unwonted manner, sometimes she would give sudden shriekes and then would burst forth into immoderate and extravagant laughter . . . as sometimes shee fell onto ye ground with it. . . . She was violent in bodily motions, leapings, strainings and strange agitations." The parson concluded that she was a Demoniacke, possessed by a Devil who "began by drawing her tongue out of her mouth most frightfully to an extraordinary length and greatness and many amazing postures of her body." We would probably say that he had written a very good description of a choreic!

Now it would seem not unlikely that the three Bures St. Mary men who took the Huntington's chorea gene to New England with them were related. Critchley ascertained from the Parish Records that the three men were in fact half-brothers, born to Mary Haste, a somewhat loose woman one must presume, exhibiting the excessive fecundity which appears in so many Huntington's chorea pedigrees. Suffolk and Essex were black spots for sorcery during the sixteenth and seventeenth centuries, and there were certainly witches in the countryside around Bures before 1630. Even to-day the incidence of Huntington's chorea in Suffolk is twelve times higher than the average for England.

The descendants of Mary Haste of Bures represent the largest family group of cases of Huntington's chorea in New England. There is, however, another large and well-known Huntingtonian family in New England. The founding member of this family first appeared

in the American colonies in 1629 or 1630, and was a well-to-do shipyard owner and hotel proprietor from Colchester—only ten miles away from Bures . . . and from Mary Haste.

After investigating 4,600 members of the New England group of Huntington's chorea, Davenport and Muncie[15] urged that immigration laws should be tightened and that routine inquiries should be made into the diseases and causes of death of the parents and grandparents of each prospective migrant. The nation should know something of the blood lines of its imported human stock as it does of its imported cattle. "Had it been known that one parent of the three brothers who came in the seventeenth century from England was

FIGURE 8

Spread of Huntington's chorea in the United States (after Davenport and Muncie, 1916).

choreic and had they been excluded on that account, we should have lost two leading educators, a surgeon or two, two state senators, two or three state assembly men, several ministers, and 900 (now about 2,500) cases of one of the most dreadful diseases that man is liable to, that does not kill quickly like cancer, nor lead rapidly to complete helplessness like paresis, but produces individuals who for half a century may know no waking hour free from forced movements, often of a violent character."

Inherited Porphyria in South Africa

Natural selection cannot operate against the Huntington's chorea allelomorph because it has no effect until the end of the reproductive life of its carrier, i.e. it has no effect on fitness. Recently, Dean[16] has uncovered an example of a gene which has increased even more spectacularly than the chorea gene, and yet produces detectable effects throughout life. This gene causes the South African form of porphyria, porphyria variegata. This disease is a defect in the synthesis of porphyrin, part of the haemoglobin molecule. It is a dominant gene, but carriers may be only detectable by their raised excretion of

porphobilinogen. However, most heterozygotes have a sensitive, easily abraded skin, particularly on the backs of the hands. More importantly, they are paralysed—often fatally—by sulphonamides and barbiturates.

This type of porphyria is very common among South Africans, both white and coloured. It has been estimated that the gene is carried by approximately 8,000 individuals alive to-day, that is three in every thousand of the white population—a very high incidence for a relatively deleterious dominant gene. It is commoner among older-established South Africans than among more recent immigrants.

Dr. Geoffrey Dean recorded the family history of all the porphyrics that he encountered. All the families which he studied came from Afrikaaner or Boer stock, although many of them had married English settlers, and had English names. In a relatively short time Dean

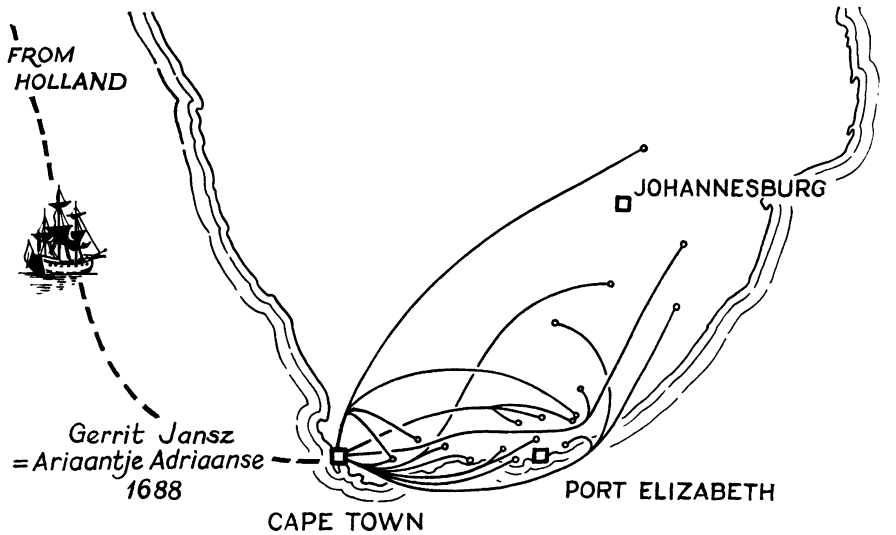

FIGURE 9

Spread of porphyria variegata in South Africa (from data given by Dean, 1963).

collected thirty-two family groups in which the porphyria gene was segregating. Many of these groups went back to a family named van Rooyen. The sensitive skin on the backs of the hands was often described as "van Rooyen skin".

The first van Rooyen was Cornelis, who came from Gorkum in Germany in 1711 and married Jacomijntje, the daughter of Gerrit, in 1720. They had eleven children, at least five of which inherited and transmitted the porphyria gene (Figure 9). However, the gene could be traced even further back in time. Other porphyric families were descended from two sisters and a brother of Jacomijntje. In other words, four of the eight children of Gerrit inherited porphyria. They must have received the gene either from Gerrit himself, or from his wife Ariaantje.

Now Gerrit came to the Cape in 1685 from Deventer in Holland and was one of the first free burghers. He was given a grant of land in the Stellenbosch district. He did not then have a wife. However, in 1687 the Lords Seventeen, a committee of seventeen directors appointed by the large cities of Holland to direct the Dutch East India Company, decided to send out orphans from Rotterdam to be wives for the free burghers at the Cape. The first eight orphans were sent out in the ship *China*, and all were married within a few weeks of arrival. Four of them married within a month. One of these was Ariaantje, who

married Gerrit. One of this couple, it is not known which, was carrying the porphyria gene. South African-type porphyria is rare in other parts of the world.

We have here, then, an example of a single mutant allelomorph which has spread to the extent that it is now carried by 8,000 people. However, the original white population of South Africa has increased even more rapidly. One million of the three million white population have the surnames of the forty original settlers. This means that the original forty burghers and their wives have increased 12,500-fold in under three centuries (the population of England has increased six-fold in the same time). The difference between the rate of increase of the gene, and the rate of increase of the population would seem to represent selection against the gene. Despite this, the relatively high frequency of the gene in the original founding population (even though it was carried by only one person), coupled with the enormous increase of population, means that porphyria variegata is very common in parts of South Africa to-day.

Inbreeding, Blindness and Tristan da Cunha

Both Huntington's chorea and porphyria variegata are caused by dominant genes. A condition caused by a recessive gene which is to-day sufficiently common to cause social and clinical problems is retinitis pigmentosa in the population of Tristan da Cunha. This disease causes progressive degeneration of the neuro-epithelium of the retina, resulting in night-blindness, followed by complete blindness by the age of 50 to 60. When the population of Tristan was evacuated to England in 1961, they were submitted to a gamut of clinical examinations. Of the 262 islanders who came to Britain, 232 were examined opthalmologically.[49] Four older individuals were reported blind. Of these, two had glaucoma, one had cataract, and one (a man of seventy-one) had retinitis pigmentosa. In addition, three younger people, a girl aged twenty-two and a brother and sister aged eighteen and sixteen respectively, all of whom knew they suffered from night blindness, were found to be suffering from earlier stages of the inherited disease.

This inherited blindness caused some popular concern at the time. Thus Mackay[36] records: "The pessimists who for generations had deplored the inbreeding were proving right: unfortunately the eyesight was impaired in some cases, and there were two (*sic*) blind persons". This seems to represent normal misapprehension about inbreeding. Inbreeding does not increase the frequency of any gene, only the proportion of homozygotes: there can be no reason to expect a deterioration in eyesight as a result of inbreeding by itself. A more likely possibility would be an increase in gene frequency due to "genetical drift".

However, this does not seem to have happened. If we assume that there has been no mutation to a retinitis pigmentosa allelomorph on Tristan, the source of the gene on the island must have been in a common ancestor of the four living homozygotes. Study of the pedigrees of the islanders shows that the gene must have originated from one of four people: William Glass, the ex-British corporal who founded the island community when he remained on the island with his South African born wife when the military garrison was withdrawn in 1817; or Thomas Swain, a Hastings-born sailor who joined the community in 1826 and married a Negress from St. Helena in the next year. One of these persons must have been heterozygous for retinitis pigmentosa. Now the majority of the genes in the present gene-pool on Tristan derive from fifteen original ancestors. Any gene present in the heterozygous condition in one of these fifteen would have a frequency of 3·3 per cent. The population increased to 262 by 1962, a seventeen-fold increase. If all the ancestors made similar contributions to the gene-pool of the present population, there must now be about seventeen retinitis pigmentosa allelomorphs in the population. There are four homozygotes, each with two genes, accounting for eight of the seventeen. The children and

unaffected parents of these four must be heterozygotes. There are nine such people, making a total of seventeen genes—as expected.[48] There are more refined ways of approaching this problem, but all give a similar solution.

Although it is impossible completely to exclude the possibility that there has been an increase in the frequency of the blindness allelomorph, there are no grounds for asserting an increase. The four afflicted Tristanians are suffering the consequences of the increase in population size on the island; it is bad luck that one of the founding members of the community was heterozygous for the gene, but since we all carry between four and eight deleterious genes on average, this is not unexpected.

Genetical Disease in the Northern Isles

Ideas about the extent to which modern populations still reflect the genetical constitution of their founders can be extended to include speculation about the hereditary nature of some diseases. The islands of the North Atlantic (Orkney, Shetland, Faeroe and Iceland) offer particularly valuable material for speculation of this sort.

The populations of these islands are Scandinavian in origin and influence: Orkney and Shetland were probably colonized in the late eighth and early ninth centuries; Faeroe and Iceland in the late ninth.

On historical grounds we should expect that the Northern Islanders should be genetically Norwegian with a large mixture of Celtic. From measurements of living Icelanders, Hannesson (cited by Coon,[12] estimated that Celts contributed 13 per cent of the gene pool of modern Iceland. About 9 per cent of Icelanders are dark-haired, and 3 per cent are red-haired. Those "traditional" genetical markers of physical anthropology (blood groups, serum proteins, etc.) which have been determined, do not discriminate very well between Norse and Celt. The frequency of the O blood group gene (I°) (Figure 10) is over 70 per cent for Iceland, Faeroes and Shetland.[7, 38, 39] Its frequency is as high or even higher for most of the west and north Highlands; the Orkney frequency is 65 per cent. There is a north and west cline in the gene in Norway, the frequencies rising from 61 per cent in the south-east to over 65 per cent in Trøndelag. I^{A} frequencies are reciprocally lower where I° is high. The frequency of *D* increases towards north Scandinavia[37]; the Northern Isles frequency is similar to that in the southern half of Scandinavia. The frequencies of the haptoglobin allelomorphs are not significantly different in Iceland, Norway, Sweden, Denmark and England.[55] There is a high frequency of PTC non-tasters in Orkney (37·7 per cent),[50] but otherwise there are no differences between England, Denmark, South Sweden and Norway, where the frequencies are all in the range 30 to 32 per cent.

As with the comparison of mouse populations discussed above, more suggestive information about population history can be gathered from multigenically determined traits. Historically, this meant craniometric data for anthropologists. We have seen that such data are now out of favour because of the difficulties of interpreting them, and the dependence of head measurements upon the environment of the growing child.[6, 17] Information which avoids these pitfalls to some extent can be derived from mortality and morbidity data on diseases which may be presumed to have a major genetical component.

Many congenital diseases fall into this category.[9] A particularly useful one is anencephaly (in which the cerebral hemispheres are replaced by vascular tissue, and the vault of the skull is completely absent), because it is invariably fatal, and the diagnosis is unmistakeable, so that it is registered as a cause of death. This condition is particularly common in central and western lowland Scotland, in South Wales, in Liverpool and in Ireland.[19, 31, 45] The whole of the rest of Britain, Denmark and the Low Countries lie in an area of medium to high frequency, while most of France and Scandinavia are in a medium

to low belt. Since 1950, the Registrar-General for Scotland has listed still-births (under which he includes anencephaly) by both cause and district. During this time the incidence of anencephaly in Orkney has been treble that in Shetland (albeit on a small number of cases), with a very similar incidence to mainland Scotland. The incidence in Shetland has been similar to that in Norway, Sweden and Iceland.

Another disease which can, it is suggested, be used for genetical comparisons, is disseminated or multiple sclerosis. This is a condition due to degeneration of the myelin sheaths in the white matter of the brain and spinal cord, resulting in a gradual deterioration of mental and locomotory abilities over a period of years. It seems to develop after encephelomyelitis infections,[35, 44] and there is probably an aetiological parallel with the disease of sheep known as scrapie.[43] Genetical differences in susceptibility are presumably

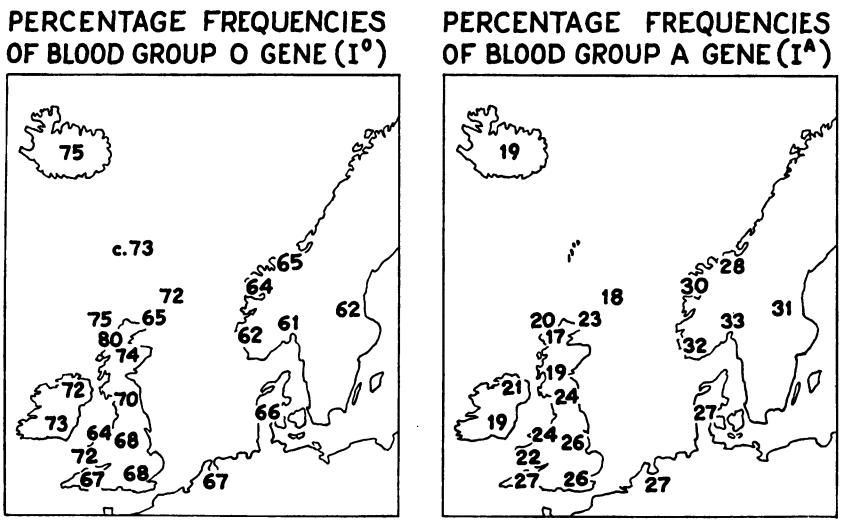

FIGURE 10

Frequencies of the O and A blood group genes in Britain, Scandinavia and the Northern Isles.

due to differences in susceptibility to infection. Certainly many sheep are resistant to scrapie, and there are plenty of examples of inherited resistance to infection in man.[30] If this is the case, it is not surprising that studies on the inheritance of multiple sclerosis have led to equivocal results.[47]

If we accept that there is a genetical element in the causation of multiple sclerosis, this would give us a simple way of accounting for the great differences in prevalence in different island groups. Shetland has the highest reported prevalence of the disease in the world (129/100,000), closely followed by Orkney.[51] In contrast, the prevalence in the Faeroes is only 54/100,000,[21] and in Iceland it is 44/100,000.[26] Following workers who urged that trace elements, and hence geology, may be significant factors in multiple sclerosis aetiology. Allison[3] has suggested that the difference in prevalence between Orkney and Shetland on the one hand and Iceland on the other could be due to the surface rocks in the different areas. However, this seems an unnecessarily complicated idea. We have seen that the genetical characteristics of founding populations may persist in a strong form in populations of mice and men. The main colonization of Orkney and Shetland was previous to and distinct from that of the Faeroese and Iceland.[54] There are marked differences in multiple sclerosis prevalence in different parts of Norway.[52] Hence we can erect a hypothesis

that the ancestors of the present populations of Orkney and Shetland carried by chance more multiple-sclerosis-predisposing genes than average, that the ancestors of the Faeroese and the Icelanders were more typical of the Scandinavian population whence they came and hence did not carry so many genes of this sort, and that these differences are reflected in the prevalence of the disease in the present populations of the islands.

Founder Effects and Natural Selection

We have seen that in a very real sense we are victims of what genes fate decreed that our fathers should have: in this way, at least, the sins of the fathers are being visited upon us their children (although the sin in the case is nothing more than their temerity in conceiving us!). However, all is not lost: natural selection is potentially strong enough to make use of the most unpromising genetical material. The Skokholm mouse population regularly has its morphological variance reduced during the winter, when four out of five animals die. In a hard winter, one of these four deaths can be regarded as being due to genetical causes, and hence to the operation of natural selection. Furthermore, on at least two occasions in the last ten years, a permanent change in the genetical composition of the population has occurred. These changes both happened following a period of rapid increase in the population, when the autumn population reached a much greater size than normal. This means that they could not be due to drift changes. They can best be interpreted as the consequences of new genotypes arising as a result of rare genetical recombinations, and the selective survival of some of these genotypes. Such an event is an adaptive change. At the moment we can only infer this through using morphological traits as genetical markers, but it is hoped that work now in progress on the cold tolerance and variability of response to temperature changes in the island mice will reveal something of the physiological causes of these genetical events.

There has been a tendency in recent years to see evolution progressing by an orderly sequence of variation favoured by natural selection being fixed as an adaptation. This has been partly due to the extremely high intensities of natural selection that have been discovered in natural populations since the war, partly due to an innate repugnance to feel that something so basic as the genetical constitution of a population owes anything to a lottery. We have seen that this simple model of evolution is, in fact, an over-simplification. Evolution may take place as a consequence of apparently inappropriate genes being delivered to start new populations. This means that evolution may take place by mistake—but the mistake may give information of value to archaeologists, anthropologists and medical epidemiologists.

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